

## UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner:

Group:

Attorney Docket # 1565

Applicant(s): HUEBLER, D., ET AL

Serial No.: 09/806,639

Filed: 04/02/2001

For : USE OF TESTOSTERONE ESTERS AND/OR  
TESTOSTERONE FOR PRODUCING BUCALLY  
APPLICABLE BIO-ADHESIVE SYSTEMS WITH  
TIME-RELEASED ACTIVE INGREDIENT

Honorable Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

May 16, 2001

Sir:

The subject application was filed without the signature of the inventors and in the German language.

Declaration papers executed by the inventors and a Certified English Translation of the application are submitted herewith.

It is respectfully requested that the required fee be charged to the account of the undersigned (19-4675).

Respectfully submitted,

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472

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USE OF TESTOSTERONE ESTERS AND/OR TESTOSTERONE FOR  
PRODUCING BUCCALLY APPLICABLE BIO-ADHESIVE SYSTEMS  
WITH TIME-RELEASED ACTIVE INGREDIENTS

IWS  
A1

The invention relates to a combination of testosterone and testosterone esters (or to the sole use of testosterone esters) in a buccal, bioadhesive preparation so that, by finely adjusted dosing of the active ingredients and ester selection, various desired plasma levels of testosterone can be set or produced in individual patients, for example to restore an endogenous circadian body rhythm.

IWS  
A2

Testosterone is quantitatively and qualitatively the most important androgen synthesized in the body. It is formed mainly in the testicles and in small amounts in the adrenal glands and in women in the ovaries. In males, testosterone is responsible for the development of the male characteristics during fetal, neonatal and pubertal maturation and finally for attaining the male phenotype and for androgen-dependent functions (for example spermatogenesis). Testosterone exerts protein-anabolic action (in muscles, bones, hematopoiesis, kidneys and liver) {E. Mutschler, "Arzneimittelwirkungen" [Drug Actions], 6th edition, pp. 334-337, Wissenschaftliche Verlagsgesellschaft mbh [publisher], Stuttgart, 1991}.

After oral or parenteral administration, testosterone is rapidly absorbed in the gastrointestinal tract. It is then transported by the portal vein to the liver where it is rapidly metabolized. As a result, the plasma half-life of testosterone is short, i.e., about 10 minutes {Auterhoff, H., Knabe, J. and Höltje, H.D., "Lehrbuch der Pharmazeutischen Chemie" [Textbook of Pharmaceutical Chemistry], 12th edition, pp. 570-573, Wissenschaftliche Verlagsgesellschaft mbh [publisher], Stuttgart, 1991}. To develop a physiological serum level, oral administration of 400 mg (!) of testosterone is needed (S.G. Johnson, E.P. Bennet and V.G. Jensen, Therapeutic effectiveness of oral testosterone, Lancet 2:1974, 1473-1475).

To prolong the action of testosterone, testosterone esters with varying chain length (testosterone propionate, testosterone enantate, testosterone undecanoate) are injected intramuscularly as an oily solution or suspension. It is known that in contact with body fluids these esters will slowly hydrolyze under the action of esterases thus releasing the pharmacologically active testosterone. The influence of the type of ester on the growth of the capon comb after i.m. injection has already been described (Meier, R. and Tschopp, E., Arch. Exptl. Pathol. Pharmacol. 226:1955, 532).

Moreover, testosterone undecanoate (in oleic acid, as a soft gelatin capsule) is administered orally via the lymphatic route [Andriol® preparation]. From the oleic acid-embedded preparation, the drug passes from the gastrointestinal tract through the thoracic duct into the lymph tract thus reaching the systemic circulation. This gives rise to varying serum levels and gastrointestinal side effects. These effects can make long-term replacement therapy difficult (A.M. Matsumoto: Hormonal therapy of male hypogonadism, Endocrinol. Metab. Clin. North Am. 23:1994, 857-875).

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Drawbacks of the aforesaid therapies are: 1. either a too short, rapidly decreasing testosterone level (after oral administration) or 2. - in the case of intramuscular injection of testosterone esters - the fact that a constantly set testosterone level cannot be changed over a long period of time (days to weeks) thus not allowing individual time control of the testosterone action. Moreover, down regulation of the basal testosterone secretion can take place.

Buccal administration of drugs is known from the prior art.

EP-0371466 A concerns a rapidly soluble tablet for fast buccal administration of steroids, among other things (for example estrogens, progestins). The main ingredient used is a water-soluble polyhydric alcohol, particularly sorbitol. The advantage is a rapid initial increase in drug concentration.

EP-0286581 A discloses the transmucosal buccal administration of estrogens (17 $\beta$ -estradiol and ethinylestradiol). The estrogen is used within the framework of hormone replacement therapy in postmenopausal women for treating PMS (postmenopausal syndrome) and for osteoporosis therapy at a dose of 50-100  $\mu$ g/day (17 $\beta$ -estradiol for PMS therapy) and at a dose of 200-400  $\mu$ g/day (17 $\beta$ -estradiol for osteoporosis therapy). Buccal administration makes it possible to attain therapeutic plasma levels by circumventing the first-pass effect.

WO-704342 describes a special formulation said to be particularly suitable for, among other things, the buccal administration of estrogens (for example estradiol and the esters of estradiol), progestins, androgens and anabolic steroids. This formulation contains a) about 1 - 20% of a soluble, adhesive polymer (carbomers, partly hydrolyzed polyvinyl alcohol [PVA], polyethylene oxide, polyacrylate, hydroxypropylmethylcellulose), b) a soluble, directly tabletted auxiliary agent and c) the active ingredient. The adhesive polymer makes the formulation or drug form adhere at the site of administration.

US-4396615-A describes the treatment of androgen-related diseases by administration of 6-methylene-progesterone, a testosterone-5 $\alpha$ -reductase inhibitor, in the form of topical formulations. Such formulations contain the inhibitor and an inert topical carrier (for example, a silicone, methylcellulose,

hydroxymethylcellulose).

CA-2105887-A discloses a bioerodable system for buccal and vaginal administration of hormones (estradiol), among other things. The system is water-soluble and mucoadherent. It consists of a solid, soluble, lyophilized foam and the active ingredient. The disintegration time is at least 8 hours. The system adheres to the mucosal membrane where it releases the drug. The polymers used are primarily gelatin, sodium carboxymethylcellulose, methylcellulose etc. A particular advantage of the system is its long adhesion time.

As regards the tailored time-release control of drugs, note that it is not possible for our currently available drugs to provide variable release of the active ingredient nor to adapt the release to the drug needs of an individual patient.

For release-control purposes, current depot drugs use passive dissolution, diffusion, swelling and erosion processes (Gröning, R., "Arzneiformen mit elektronisch gesteuerter Freisetzung" [Drug Forms with Electronically Controlled Release], in "Pharmazeutische Technologie: Moderne Arzneiformen" [Pharmaceutical Technology: Modern Drug Forms], p. 441, ed. [sic - Translator], Müller, R.H. and Hildebrand, G.E. (editors), Wissenschaftliche Verlagsgesellschaft mbh (publisher), Stuttgart, 1998).

The time-controlled release of drugs is also known from the prior art.

JP-07118143 discloses time-controlled capsules which a) are water-insoluble or partly water-soluble, b) consist of water-swelling substances (powder, granulates or pills of, for example, calcium carboxymethylcellulose or polyvinylpyrrolidone) and c) contain elements (tablets) with the active ingredient in the center of the capsule.

The prior art also describes sustained-release preparations using polymers. Thus EP-068446, for example, discloses the use of methylcellulose or carboxymethylcellulose in sustained-release mixtures.

INS  
P3 The object of the present invention is to make use of the advantages of buccal administration of steroids with high first-pass effect and low bioavailability, especially of testosterone and the esters thereof, by exploiting the different pharmacokinetics of the various testosterone esters (depending on chain length), so as to be able, by careful selection of appropriate dosages and esters, to attain a desired drug profile.

This objective is reached by use of testosterone esters with 1 to 20 carbon atoms in the carboxylic acid radical or of a mixture of two or more testosterone esters with different carboxylic acid radicals and/or testosterone, for the preparation of buccally administered bioadhesive systems with time-controlled release of the active ingredient, for treating diseases associated with a modified testosterone level.

Preferably used are testosterone esters wherein the carbon structure of the carboxylic acid radical is linear, branched, alicyclic, saturated and/or unsaturated and contains up to five double and/or triple bonds.

Also preferred is a ratio of testosterone to testosterone ester from 1 : 100 to 1 : 1 and particularly from 1 : 10 to 1 : 1.5.

It is particularly preferred that the buccally administered bioadhesive systems be prepared by first embedding into an organic polymer the active ingredients, separately or together, in an amorphous state as obtained by use of a spray-drying process.

It is especially preferred to mix the amorphous, spray-dried testosterone products with other auxiliary agents, binders, fillers, lubricants, bioadhesive polymers, surfactants or disintegration accelerators and to compress the mixture into single-layer or multilayer tablets.

The use for a tailored adjustment of therapeutic and/or circadian rhythms of the testosterone levels is preferred.

Surprisingly, we have now found that the chain length of the testosterone ester not only determines the solubility, but, as was shown experimentally, evidently also the kinetics of ester cleavage in the blood or tissue fluids by the corresponding hydrolases. Note in particular, when testosterone esters are employed, the use of the embedding technique of spray-drying in organic polymers (polyvinylpyrrolidone, hydroxypropylmethylcellulose, solid polyethylene glycols) to achieve improved solubility in the oral cavity. This is particularly important in view of the small saliva volumes (about 1 - 1.5 mL) which here, on the average, are available for the dissolution of sparingly soluble esters. In the publication by Jody Voorspoels (Voorspoels, J., Remon, J.P., Eechaute, W.E. and De Sy, W., Buccal Absorption of Testosterone and Its Esters Using a Bioadhesive Tablet in Dogs, Pharmaceutical Research, vol. 13, No. 8, 1996, 1228-1232), the testosterone esters (testosterone acetate, testosterone propionate, testosterone enantate, testosterone decanoate) studied in six castrated beagle dogs did not show a higher bioavailability than testosterone in spite of their higher lipophilicity. Because the esters were directly compressed only after dry mixing, without using a special premixing technology (amorphization by spray-drying), these poorer results presumably are due to the low, and in some cases extremely low, solubility of the esters in the crystalline state.

We were able to show that by the use of buccal administration of testosterone in combination with testosterone esters of different chain length, it is possible to attain different blood level patterns or rhythms (such as a circadian rhythm). In selecting the testosterone ester, the choice can be made specifically from three groups: 1. esters of shorter chain length (for example, testosterone acetate or propionate), 2. esters of medium chain length (for example testosterone enantate, cypionate or cyclohexanecarboxylate) and 3. esters of higher chain length (for example testosterone undecanoate, or

bucyclate).

According to the invention, this objective is reached by dissolving testosterone or the particular testosterone ester together with the polymer (for example polyvinylpyrrolidone or hydroxypropyl-methylcellulose) in ethanol and processing the mixtures further in a spray-drying unit to form an amorphous, embedded, spray-dried formulation. It is possible in this case 1) to embed said active ingredients separately from each other or 2) to embed them together in a single processing step, to obtain an amorphous mixture.

The fine-particle embedded spray-dried material is then subjected to dry mixing with other auxiliary agents for making bioadhesive buccal tablets [binders: polyvinylpyrrolidone, cellulose ethers; fillers: Cellactose®, mannitol, sorbitol, lactose; lubricants: magnesium stearate, hydrogenated vegetable fats; bioadhesive polymers: polyacrylates (Carbopols®, sodium carboxymethylcellulose) and optionally other auxiliary agents, such as surfactants or disintegration accelerators]. The mixture is then compressed into buccal tablets which can have a layered structure (active ingredient layer, bioadhesive layer; unidirectional or multidirectional release).

Based on blood level studies with the individual drug components alone, it is possible to attain the appropriate release patterns by changing the following two parameters

- dosage of the active ingredient
- selection of the ester or of the chain length at C-17.

An advantageous combination is, for example, that of the short-acting testosterone with testosterone undecanoate (eleven-carbon chain) which has a longer half-life (see practical examples).

To this end, an advantageous ratio of the active ingredients, namely of testosterone to  $\Sigma$  testosterone esters, is from 1 : 100 to 1 : 1 and particularly from 1 : 10 to 1 : 1.5.

By skillful combination of testosterone with testosterone esters, it is possible to attain blood level patterns which are capable of recreating or simulating the body's own rhythmicity of endogenous testosterone levels. For example, the duration of action of a bioadhesive buccal tablet with testosterone can be prolonged by combining testosterone with testosterone undecanoate (cf. Fig. 1 and Fig. 3). In the practical example (equimolar combination), the duration of blood levels of > 100 ng/mL is increased in female dogs from 2 to 4 hours. Moreover, a marked (slower) pulse is reached with a maximum appearing after about 3 hours. After 8 h, the testosterone values of nearly 50 ng/mL are still double as high as those attained with testosterone alone.

In essence, the set blood level pattern of testosterone is controlled through two parameters:

- \* The chain length and steric structure of the ester chain at C-17. This structure determines, on the one hand, the lipophilicity and thus the solubility and, on the other, in a pronounced manner, the rate of ester cleavage and hydrolysis (interactions of the ester side chain with the active center of hydrolases). For example, esters with a longer chain length are cleaved more slowly than those with an intermediate or shorter chain length. In this sense, the released testosterone becomes available more slowly than after administration of pure testosterone, i.e. the peak appears later. Through the chain length, it is thus possible to attain a more or less tailored time control of therapeutic action.
- \* The dosage of testosterone or of the testosterone esters on the basis of direct proportionality between the area under the curve [AUC] and the dose given.

This could be important for hormone replacement therapy in elderly men with partial androgen deficiency (PADAM patients) in that a deficient plasma level could be appropriately corrected.

The following practical examples illustrate the invention without limiting its scope.

### EXAMPLE 1

#### Bioadhesive Tablet with Testosterone

#### Formulation

Component	Weight/tablet
<b>Active ingredient layer</b>	
Testosterone premix (20%)	50.00
Mannitol	43.90
Cellactose 80	29.50
Carmellose sodium	1.20
Magnesium stearate	1.50
Talc	4.50
<b>Adhesive layer</b>	
Mannitol	17.40
Cellactose 80	34.82
Carmellose sodium	10.18
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

## Preparation:

### Preparation of the Premix

The testosterone premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose) and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to obtain a fine powder.

### Preparation of the Active Ingredient Layer

This premix was mixed with the other auxiliary agents for the active ingredient layer (mannitol, Cellactose 80) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carmellose sodium, magnesium stearate, talc) was then added, and mixing was continued for 5 minutes.

### Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Cellalactose 80 were mixed for about 20 min. The ground colored mixture, Carmellose sodium and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tableting press to form two-layer tablets.

Fig. 1 shows the blood level variation for a formulation according to Example 1.

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**EXAMPLE 2****Bioadhesive Tablet with Testosterone Undecanoate****Formulation**

Component	Weight/tablet
<b>Active ingredient layer</b>	
Testosterone undecanoate premix (20%)	50.00
Mannitol	43.90
Cellactose 80	29.50
Carmellose sodium	1.20
Magnesium stearate	1.50
Talc	4.30
<b>Adhesive layer</b>	
Mannitol	17.40
Cellactose 80	34.82
Carmellose sodium	10.18
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

**Preparation:****Preparation of the Premix**

The testosterone undecanoate premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose) and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to obtain a fine powder.

**Preparation of the Active Ingredient Layer**

This premix was mixed with other auxiliary agents for the active ingredient layer (mannitol, Cellactose 80) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carmellose sodium, magnesium stearate, talc) was then added, and mixing was

continued for 5 minutes.

#### Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Cellalactose 80 were mixed for about 20 min. The ground colored mixture, Carmellose sodium and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tableting press to obtain two-layer tablets.

Fig. 2 shows the blood level variation for a formulation according to Example 2

### EXAMPLE 3

#### Bioadhesive Tablet with Testosterone and Testosterone Undecanoate

#### Formulation

Component	Weight/tablet
<b>Active ingredient layer</b>	
Testosterone/ testosterone undecanoate premix (20%, 20%)	50.00
Mannitol	43.90
Cellactose 80	29.50
Carmellose sodium	1.20
Magnesium stearate	1.50
Talc	4.30
<b>Adhesive layer</b>	
Mannitol	17.40
Cellactose 80	34.82
Carmellose sodium	10.18
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

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### Preparation of the Premix

The testosterone/testosterone undecanoate premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose) and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to obtain a fine powder.

### Preparation of the Active Ingredient Layer

This premix was mixed with other auxiliary agents for the active ingredient layer (mannitol, Cellactose 80) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carmellose sodium, magnesium stearate, talc) was then added, and mixing was continued for 5 minutes.

### Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Cellalactose 80 were mixed for about 20 min. The ground colored mixture, Carmellose sodium and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tableting press to form two-layer tablets.

Fig. 3 shows the blood level variation for a formulation according to Example 3.

**EXAMPLE 4****Bioadhesive Tablet with Testosterone and Testosterone Enantate****Formulation**

Component	Weight/tablet
<b>Active ingredient layer</b>	
Testosterone/ testosterone enantate premix (20%, 20%)	50.00
Mannitol	58.60
Emcompress	14.00
Carbopol® 974	2.00
Magnesium stearate	1.50
Talc	4.30
<b>Adhesive layer</b>	
Mannitol	17.40
Emcompress	34.82
Carbopol® 974	13.00
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

**Preparation:****Preparation of the Premix**

The testosterone/testosterone enantate premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to form a fine powder.

**Preparation of the Active Ingredient Layer**

This premix was mixed with other auxiliary agents for the active ingredient layer (mannitol, Emcompress) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carbopol® 974, magnesium stearate, talc) was then added, and mixing

was continued for 5 minutes.

#### Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Emcompress were mixed for about 20 min. The ground colored mixture, Carbopol® 974 and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tableting press to form two-layer tablets.

### EXAMPLE 5

#### Bioadhesive Tablet with Testosterone Propionate and Testosterone Undecanoate

##### Formulation

Component	Weight/tablet
<b>Active ingredient layer</b>	
Testosterone propionate/ testosterone enantate premix (20%, 20%)	50.00
Mannitol	58.60
Emcompress	14.00
Carbopol® 974	2.00
Magnesium stearate	1.50
Talc	4.30
<b>Adhesive layer</b>	
Mannitol	17.40
Emcompress	34.82
Carbopol® 974	13.00
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

### Preparation of the Premix

### Preparation of the Active Ingredient Layer

### Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Emcompress were mixed for about 20 min. The ground colored mixture, Carbopol® 974 and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tableting press to form two-layer tablets.